QUINOLINE DERIVATIVES CONTAINING ARSENIC

BY

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY

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BE ACCEPTED AS FULFILLING THIS PART OF THE REQUIREMENTS FOR

THE DEGREE OF Doctor of Philosophy in Chemistry

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The writer wishes to express his
sincere thanks and appreciation
to Professor Roger Adams.

I. INTRODUCTION

This investigation was undertaken with the object of studying new organic derivatives of arsenic which might possess valuable therapeutic properties, and to develop a substance which would be superior to Arsphenamine[*] in the treatment of diseases caused by trypanosomes and spirochetes.

This field of chemotherapy was opened up by Ehrlich and Bertheim in 1907, and several years later they developed Salvarsan and Neosalvarsan, two substances which have proved to be very valuable therapeutic materials. Since the development of these substances several hundred new organic arsenic compounds have been prepared, but none has displaced Salvarsan and Neosalvarsan. Recent clinical work has given evidence that these substances are far from ideal, and it is well known that the advanced stages of syphilis cannot be cured by the application of these materials.

Previous observation has shown that in order to possess trypanocidal action the organic arsenical must contain nitrogen in some form; further, that nitrogen atoms covered by certain organic radicals are more active than free amino groups, and that the substances are in general more stable, and consequently less toxic.

From these considerations it was decided to take up the preparation of arsenicals containing tertiary nitrogen in a ring system, particularly in the quinoline grouping. This nucleus is present in many of the common alkaloids and in other substances

[*] The official American Name for "Salvarsan".

which are physiologically active.

The preparation of quinoline derivatives containing arsenic was the subject of a paper by Fränkel[1] and Löwy in 1913, and these investigators applied many general reactions without success. They were able, however, by applying the Döbner-Miller quinaldine synthesis, to obtain small quantities of a substance which they formulated as quinaldine-6-arsonic acid. By reduction with sodium amalgam they obtained a substance which corresponded to quinaldine-6-arsenious oxide. These substances were obtained in such small quantities that the authors were unable to make a thorough investigation of them, and it appears uncertain that they were really quinaldine arsenic derivatives.

Since the quinaldine synthesis mentioned yielded an arsenic containing product, it seemed worth while to investigate the closely related Döbner cinchoninic acid synthesis with the idea of preparing cinchoninic acid derivatives containing arsenic.

II. THEORETICAL PART

In considering the synthesis of quinoline derivatives containing arsenic there appeared to be two ways of attacking the problem: the direct method, starting with a quinoline nucleus already formed and introducing arsenic into the molecule, and the indirect method, building a quinoline ring into a molecule already containing arsenic.

A. General Resumé of Methods

There are a number of ways which were deemed applicable for the introduction of arsenic into the quinoline molecule. Of these the following were considered:

The Bechamp Reaction: This has proved valuable for the arsenation of aryl amines, and of indole[2] derivatives:
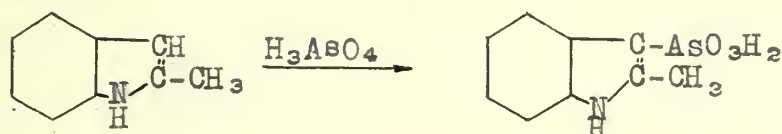
Fränkel[1] and Löwy applied this method to quinoline, and tetrahydroquinoline, but were unable to obtain the desired arsonic acids even on heating to $200°$ under pressure.

Direct Arsenation with Arsenic Chloride: This had led to a number of p-alkylaminophenyl arsenious chlorides from the corresponding mono and dialkylanilines and arsenic chloride[3]
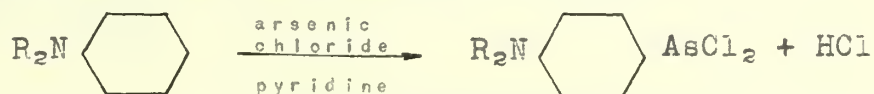

By the treatment of quinoline, 8-hydroxy quinoline, and tetrahydroquinoline with arsenic chloride, Fränkel and Löwy obtained addition compounds which on treatment with water liberated arsenic tri-

oxide; the arsenic chloride could not be introduced into the ring by treatment of the addition compounds with aluminum chloride.

Interaction of Arsenic chloride, an aryl halide and metallic sodium: This reaction was used by Michaelis[4] for the synthesis of a large number of arsenic compounds, but the reaction does not run smoothly and is only used at the present time in a few instances.

The Bart Reaction[5]: An aryl amino group is replaced by the arsonic acid grouping through the diazo compound, by treating with sodium arsenite:
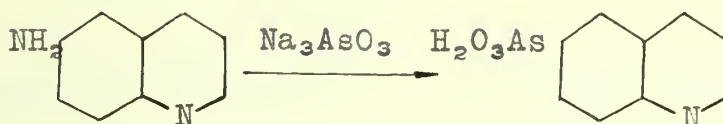
The Meyer Reaction[6]: The treatment of alkyl halides with sodium arsenite proved to be a valuable means of obtaining aliphatic arsonic acids. Since halogens in the 2- and 4-positions in the quinoline ring are aliphatic in character, it might be possible to apply the Meyer reaction. Certainly compounds of the type (b)

a.

b.
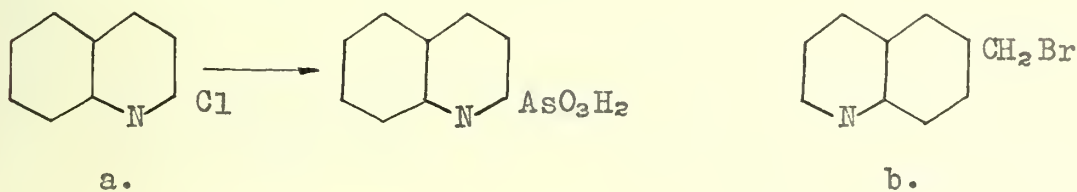
would be expected to react with sodium arsenite to give quinolyl methyl arsonic acids.

Indirect Syntheses.

In the literature is reported a large number of syntheses of quinoline and its derivatives in which the pyridin

ring is closed onto a benzene nucleus. Of these the following were considered to be of possible application to compounds containing arsenic.

Skraup's synthesis[7]: The treatment of an aromatic amine with glycerol, sulfuric acid and an oxidizing agent has given a large number of quinoline derivatives, and the reaction has proved to be quite general. If p-arsanilic acid were used in this reaction it would be expected that quinoline-6-arsonic acid would result, but it was found by Fränkel and Löwy that the arsenic was split off and only quinoline resulted.

Knorr's synthesis[8] from aniline and acetoacetic ester:

$$CH_3COCH_2CO_2R$$
thru the anilide
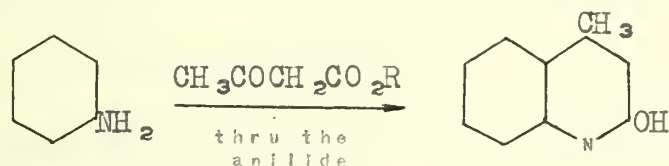
This reaction was applied to arsanilic acid and did not give the desired product[1].

Kulisch's synthesis[9] from o-toluidine and glyoxal:

$$+ 2H_2O$$

35 - 40% yields.
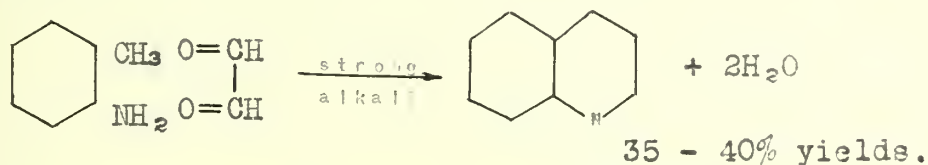
The Döbner-Miller quinaldine synthesis[10]: This reaction was used by Fränkel and Löwy and they obtained a product which they stated to be quinaldine-6-arsonic acid. It is rather surprising, how-

* A repition of this reaction gave large quantities of quinoline, but the formation of a crystalline picrate, decomposing from 260-275°, led to the belief that some quinoline-6-arsonic acid was present in the reaction mixture altho it could not be isolated as such.

ever, that their product was insoluble in alkalies and in acids, and from analogy one would expect the compound mentioned to be soluble in both of these reagents.

On reduction with sodium amalgam they obtained a compound soluble in alkalies which they stated to be the corresponding arsenious oxide.

Döbner's cinchoninic acid synthesis[11]. This reaction is of general application and is taken up in detail later.
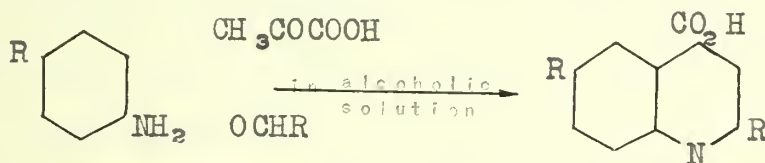
Friedlander's synthesis[12] and its extensions: Although the synthesis of quinoline derivatives from o-aminobenzaldehyde itself
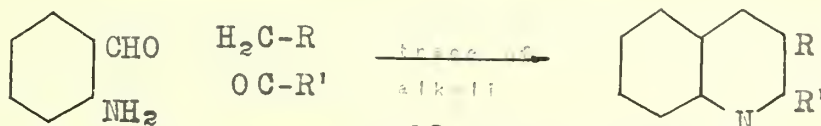
is not practical, certain extensions[13,14] have proved to be quite valuable means of synthesizing quinoline derivatives:
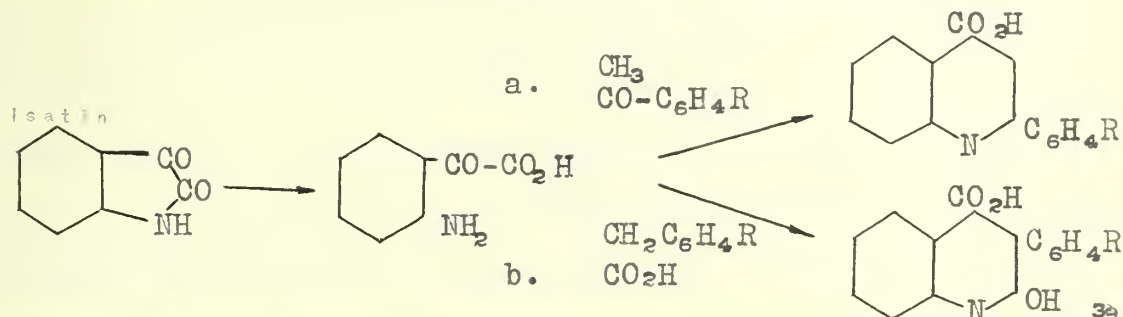
Since this work was started, two substances of the types (a) and (b) have been prepared with the arsonic acid grouping in the p-position.[40] It seems likely that cinchoninic acid derivatives could

readily be prepared from these substances by application of the above reactions.

After a consideration of the above reactions and the possibilities offered, it appeared that the most promising methods of obtaining quinoline derivatives containing arsenic were the Bart reaction and the Döbner cinchonic acid synthesis.

B. The Bart Reaction

For trying this reaction 6-aminoquinoline was diazotized and treated with sodium arsenite according to the usual procedure. Although an evolution of nitrogen occurred on mixing the diazo- and arsenite solutions, no quinoline arsonic acid could be isolated from the material. Since the Bart reaction has proved to be quite general for all substituted types of aromatic amines it seemed unusual that the quinoline arsonic acid was not obtained by this method. It is noted, however, that Schmidt[15] used o- and p-aminodiphenyl and obtained tarry brown substances from which the arsonic acids could not be isolated.

C. The Döbner Cinchoninic Acid Synthesis.

The condensation of aromatic amines with pyruvic acid and aldehydes in alcoholic solution has led to the production of a large number of 2-substituted quinoline-4-carboxylic acids. This reaction has been found to be quite general for aryl amines and almost unlimited in its applications. The following examples indicate the many types of aromatic amines which have been converted into the corresponding cinchoninic acids: the toluidines, aminophenols and their ethers, anthranilic acid, m- and p-halo-

genated anilines[16], m- and p-aminoacetophenone[16], p-aminoacet-
anilide[18], benzidine[19], and the naphthyl amines. The reaction
seems to be even more general for aldehydes than amines, since
both aromatic and aliphatic aldehydes, including formaldehyde and
furfural, will give cinchoninic acids.

In a number of cases the yields in this condensation
are unsatisfactory, and this is due to the formation of hydrogen-
ated by-products and a group of alkali insoluble substances. The
nature of the latter was investigated by Döbner[11], and by Garza-
rolli-Thurnlackh[17], who assigned to them the formula of the anil
of a diketopyrrolidine derivative:

$$\text{N} \begin{matrix} \text{CO-C=N} \\ | \quad | \\ \text{CH-CH}_2 \\ \text{C}_6\text{H}_5 \end{matrix}$$
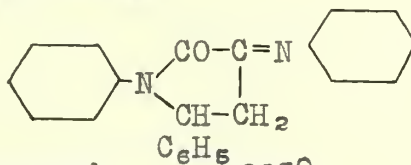
Döbner's "anil" compound, m.p. 335°.

It was noted that the solvent plays an important part in determin-
ing the course of the condensation. Alcohol favors cinchoninic
acid formation, whereas ether and benzene lead almost exclusively
to the anils of diketopyrrolidines. It was also found that the
substitution of esters of pyruvic acid led to the diketopyrroli-
dine anil.

The most comprehensive study of the limitations of this
reaction was made by Borsche[16], who studied the effect of substitu-
ents in all three of the reactants. The results of this and
previous investigations may be stated briefly as follows:

i. The introduction of methyl or hydroxy groups into
the m-position in the aryl amines increased the yield of cinchon-
inic acid, due to its activating effect on the hydrogen in the
o-position to the amino group. This activating effect seemed to

be at a maximum in β-naphthylamine, from which no diketopyrroli-
dine derivative could be obtained even when ether was used as the
solvent. The reaction with the nitroanilines went exclusively to
the diketopyrrolidines, and from these amines no cinchoninic acids
could be obtained under the most favorable circumstances.

ii. The reaction is a general one for aldehydes, and
with the use of β-naphthylamine especially, cinchoninic acids can
be obtained from all aldehydes. This reaction had previously been
proposed by Döbner[20] as a specific reaction for all aldehydes.

iii. The introduction of phenyl, o-nitrophenyl and
benzoyl groups into the pyruvic acid molecule caused the reaction
to run chiefly to diketopyrrolidine derivatives in the case of the
simple aryl amines. With β-naphthylamine, however, the usual cin-
choninic acids were formed. The introduction of the benzyl group
into the pyruvic acid rest led to the usual mixture of both sub-
stances, but the diketopyrrolidine derivative predominates in the
case of the simple aryl amines.

When arsanilic acid, benzaldehyde, and pyruvic acid are
heated together in absolute alcoholic solution, a condensation
product is obtained in good yields. The composition of this sub-
stance corresponds to that of a cinchoninic acid, I, or a simple
diketopyrrolidine derivative, II:

H_2O_3As ... CO_2H

I. $C_{16}H_{12}O_5NAs$

II. ... CO-CO / CH-CH$_2$ ... C_6H_5 $C_{16}H_{14}O_5NAs$
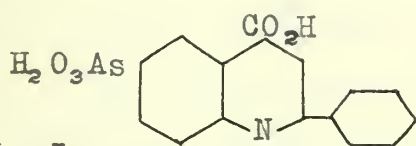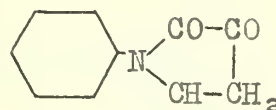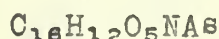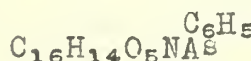
The usual separation of these substances by the solution of the

cinchoninic acid in alkalies cannot be applied since an alkali soluble group is already present in the molecule. In order to determine the structure of the substance a study was made of its reactions.

The condensation product is unstable toward hot mineral acids, and therefore the usual reaction of replacing the arsonic acid group by iodine, and identification of the resulting iodo-compound cannot be applied. It was found that the compound gave off approximately one mole of carbon dioxide on heating to its decomposition point. This was considered to be evidence for the cinchoninic acid structure since it is well known that these substances readily lose one mole of carbon dioxide on heating above their melting points.

It was thought likely that a fusion of the substance with sodium hydroxide would give additional evidence, since the 2-phenylquinoline-4-carboxylic acid-6-arsonic acid, I, would be expected to give either 2-phenyl quinoline or 2-phenyl 6-hydroxy quinoline under this treatment. It was found, however, that the chief nitrogenous product from the alkaline fusion was aniline. This could hardly be explained on the cinchoninic acid formula, and the formation of carbon dioxide is difficult to explain on the diketopyrrolidine formula. It was therefore decided to prepare a diketopyrrolidine derivative and determine whether it gave carbon dioxide on heating.

For this purpose the simple diketopyrrolidine, III, prepared from p-nitraniline[16] was used, and it was found that on

$$NO_2 \langle \rangle NH_2 \quad \xrightarrow[\substack{alcoholic \\ solution}]{\substack{CH_3COCOOH \\ C_6H_5CHO}} \quad NO_2 \langle \rangle N \begin{array}{c} CO-CO \\ | \\ CH-CH_2 \\ C_6H_5 \end{array}$$
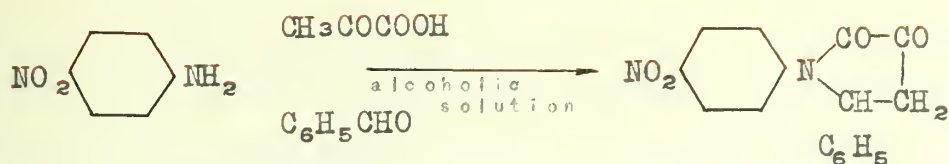
III.

heating this substance in boiling ethyl benzoate for fifteen minutes 63% of one mole of carbon dioxide was evolved. To determine the effect of the arsonic acid grouping a sample was mixed with nitrophenyl arsonic acid and heated in boiling ethyl benzoate under the same conditions. In this case the amount of carbon dioxide amounted to 95% of one mole.

These results, together with the behavior on alkaline fusion, indicate that the first conclusion was incorrect, and that the compound is not a quinoline arsonic acid. This conclusion is supported by the fact that the same condensation product is obtained when the reaction is carried out in ethereal suspension, and also when the ethyl ester of pyruvic acid is substituted for the free acid. In both of these cases the diketopyrrolidine derivatives would be expected, and the product proved to be identical with the original condensation product.

Since the evidence for the diketopyrrolidine is based only on the analogy to p-nitraniline, it seemed advisable to conduct further experiments. It would be expected that the 4-keto group would easily form an anil with an aromatic amine, leading to compounds of the type IV, containing the arsonic acid grouping:

$$R \langle \rangle N \begin{array}{c} {}^{5}CO-CO{}^{4} \\ | \\ CH-CH_2 \\ C_6H_5 \end{array} \quad \longrightarrow \quad R \langle \rangle N \begin{array}{c} CO-C=N \langle \rangle \\ | \\ CH-CH_2 \\ C_6H_5 \end{array}$$
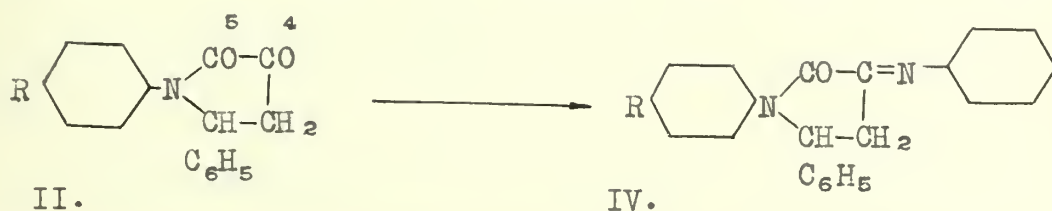
II.   IV.

One would expect this reaction to take place very readily, since
compounds of the type IV are usually formed as by-products when
the Döbner cinchoninic acid synthesis is carried out.

In order to prepare this anil the condensation product
was dissolved in boiling alcohol and treated with one mole of
aniline. From the reaction mixture a product was obtained which
was insoluble in boiling 10% sodium hydroxide and melted from
147°-148°. The insolubility in sodium hydroxide indicated that
the substance no longer contained the arsonic acid grouping and
could not be the desired anil.

A review was made of the literature on the addition of
pyruvic acid to benzylidene aniline, and it was noted that Schiff[21]
had carried out the reaction in benzene solution. In this way he
obtained a compound melting at 147°, which he gave the formula:

$$C_6H_5N=CH-C_6H_5 + CH_3COCO_2H \longrightarrow$$
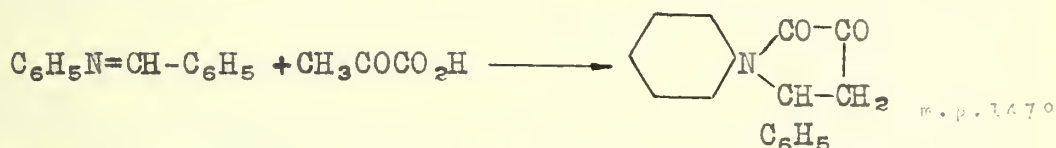
and it seemed possible that the alkali insoluble substance men-
tioned above was identical with Schiff's compound.

Garzarolli-Thurnlackh[17] on repeating the work of
Schiff, obtained the compound m.p. 147°-148°, along with larger
quantities of Döbner's anil compound, m.p. 225°. It seemed likely,
therefore, that by using an excess of aniline the Döbner anil com-
pound could be obtained from the arsanilic acid condensation
product. The latter was treated with two and one half moles of
aniline and gave arsanilic acid, but none of the anil could be
isolated.

The behavior of the condensation product on treatment

with sodium hydroxide is worthy of mention. The material dis-
solves readily in one mole of aqueous sodium hydroxide to a clear
yellow solution, which on standing at room temperature deposits a
white precipitate. The solution has a strong odor of benzaldehyde,
and is acid in reaction to litmus paper. The precipitate contains
arsenic and is soluble in alkalies; it is very difficult to purify
and the impure material melted with decomposition from 140°-150°.
With two or more moles of alkali the condensation product dissolves
to a clear yellow solution which does not become turbid or deposit
any precipitate.

Since the reactions enumerated could not be adequately
explained on the basis of the diketopyrrolidine formula, II, a
consideration was made of other isomers and the following was
suggested, formula V:
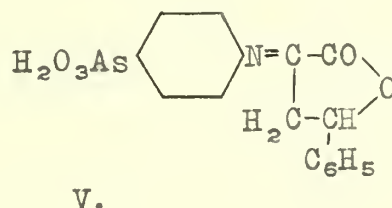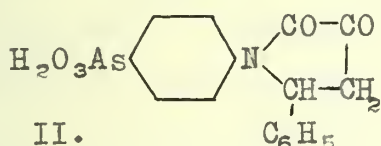
Although no compounds of this structure are described in the
literature, it was noticed that a compound of this type was sug-
gested as a hypothetical intermediate in the formation of Döbner's
anil compound according to the following mechanism[17]:
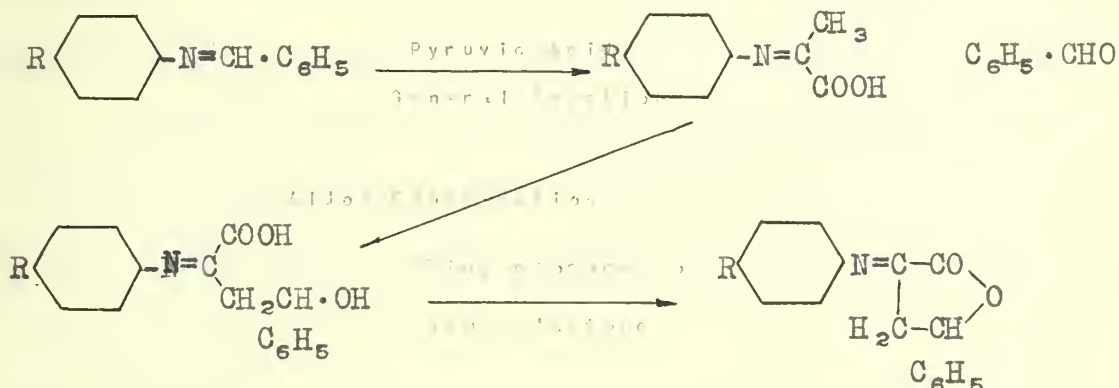
If the condensation product from arsanilic acid has the structure
V, it will be the first compound of this type to be isolated and
it may give additional information concerning the course of the
reaction between aryl amines, pyruvic acid and aromatic aldehydes.

In conclusion, it may be said that altho the structure
of the compound formed by the condensation of arsanilic acid with
pyruvic acid and benzaldehyde has not been definitely established,
between formulae II and V, the formation of one mole of carbon
dioxide on heating, the splitting off of aniline on alkaline
fusion and the regeneration of arsanilic acid on treatment with
aniline, are facts which are more easily explained on the basis
of the latter.

Limitations of the Reaction

With the idea of studying the limitations of the re-
action between aminoaryl arsonic acids, aldehydes and pyruvic acid,
a series of reactions was carried out between substituted arsan-
ilic acids and aldehydes with pyruvic acid.

It was found that arsanilic acid and pyruvic acid
yielded the desired condensation products with all of the aromatic
aldehydes tried. These included o- and p-methoxy, p-halogenated,
p-dimethylamino, and o-nitrobenzaldehyde[33]. No condensation products
were obtained from paraldehyde and n-butyraldehyde.

When o-substituted aminoaryl arsonic acids were used
a condensation took place to give benzylidene derivatives of the
amine, but these did not react further with the pyruvic acid even

on long heating. The substances used for these experiments were o-arsanilic acid, 3-methyl-4-aminophenyl arsonic acid, and 3-bromo-4-aminophenyl arsonic acid. These results are in accord with those of Borsche, who was unable to obtain condensation products from o-chloro, and o-nitroaniline[16].

When m-substituted aminoaryl arsonic acids were used the condensation occurred in the usual manner, and good yields of the desired products were obtained. The particular acids used for these experiments were 2-methyl-4-aminophenyl arsonic acid, and 3-methoxy-4-aminophenyl arsonic acid.

These experiments lead to the following generalizations:

i. The reaction is general for aromatic aldehydes, but not for the simple aliphatic aldehydes.

ii. The reaction takes place with substituents in the m- and p-positions in the aminoaryl arsonic acid, but does not occur when o-substituents are present. In the latter instance, benzylidene derivatives are formed which do not react further.

III. EXPERIMENTAL PART

The experimental work is divided into three parts: first, the preparation of substituted aromatic arsonic acids; second, the condensation of aminoaryl arsonic acids with aldehydes and pyruvic acid; third, the constitution and reactions of the condensation products.

A. The Preparation of Arsonic Acids by the Bart Reaction

This reaction has been extensively used for the synthesis of aromatic arsonic and arsinic acids, and various modifications have been used in specific cases. For the nitro substituted amines, the procedure of Schmidt[15] is found to be quite satisfactory and was used in preference to that of Jacobs, Heidelberger and Rolf[22]. The yields have been found to vary considerably when only slight changes were made in the procedure. For this reason the method employed is given in detail.

General Procedure: 1 mole of the amine was dissolved (or suspended) in 600 cc. of 5-N hydrochloric acid (3 moles), chilled by the addition of ice, and diazotized by introducing a solution of 1 mole of sodium nitrite through a dropping funnel extending below the surface of the liquid. With good stirring the nitro-amines dissolve almost completely in the course of 10 - 15 minutes. The diazo-solution was filtered from any insoluble material and transferred to a large container of 12-15 liters capacity. It was thoroughly chilled by the addition of ice, and a few cc. of isoamyl acetate added to cut down the frothing when the arsenite was added later.

With good stirring 300 cc. of 5-N sodium hydroxide
(1 mole) was added, followed at once by a mixture of 750 cc. of
3-N sodium arsenite solution, Na_2HAsO_3, 60 cc. of 5-N hydrochloric
acid, 650 cc. water, 650 g. ice and 200 cc. of 20% copper sulfate
solution, added immediately before using. The addition of the
copper sulfate caused the formation of a green precipitate in the
arsenite solution. When the arsenite solution was added a vigor-
ous evolution of nitrogen occurred and unless the reaction mixture
was thoroughly agitated the froth almost filled the container.
After allowing the mixture to stand for an hour it was warmed to
40-50° and filtered. The clear filtrate, which was neutral or
slightly alkaline in reaction, was acidified to litmus with acetic
acid, concentrated on a steam bath and filtered hot to remove a
yellow flocculent by-product. The filtrate was treated with hydro-
chloric acid until acid to Congo paper and the arsonic acid
separated out. The precipitate was filtered with suction and
washed thoroughly with water. For most purposes the crude product
is sufficiently pure without further treatment.

Prepared by dissolving 198 g. of arsenic trioxide in 800 cc. of
5-N sodium hydroxide, and diluting to 1000 cc.

Attempt to prepare Quinoline-6-Arsonic Acid: 6-Nitroquinoline was
prepared by the method of Knueppel[7], from p-nitranilin, glycerol,
arsenic pentoxide and sulfuric acid. For reduction to the amine
it was found advisable to use the purified nitro-compound and not
attempt to reduce the crude product.

The reduction of 6-nitroquinoline to 6-aminoquinoline
was effected by means of powdered iron [23] and a small amount of
acid. The crude dark product was purified by vacuum distillation,
and the product was obtained in pale yellow crystals which darkened

on exposure to the air. From 35 g. of nitroquinoline, the yield of amine, b.p. 169°-176° at 5-6 mm., was 18-20 g. which is 60-70% of the theoretical.

15 g. of 6-aminoquinoline was diazotized and treated with sodium arsenite according to the above procedure; an evolution of nitrogen occurred and a thick brown material was formed. From the filtrate after concentration and careful neutralization no quinoline arsonic acid could be isolated. On evaporating to dryness and extracting the salt with alcohol, no arsonic acid could be obtained from the alcoholic extract. The reaction was repeated with the same result, and was then given up.

2-Nitrophenyl Arsonic Acid:[22] 28 g. of pure o-nitraniline was finely pulverized and diazotized at 10°, and the diazo-solution treated with sodium arsenite according to the general directions. The product separated out in pale yellow-white needles. The yields were good, varying from 38-43 g., which is 75-85% of the theoretical. The product was sufficiently pure for reduction without further purification.

4-Nitrophenyl Arsonic Acid[22]: 28 g. of technical p-nitraniline was diazotized at 10° and treated in the usual manner. The p-nitrophenyl arsonic acid was obtained in the form of pale yellow crystals weighing 28 g. or 56% of the theoretical amount. This is slightly better than that claimed by Jacobs, Heidelberger and Rolf.

2-Methoxyphenyl Arsonic Acid: 12.3 g. of pure o-anisidine was diazotized at 0° and treated according to the general procedure. The crude o-anisyl arsonic acid separated in slightly yellow

flocks and after drying weighed $15\frac{1}{2}$ g. which is 65% of the theor-
etical amount. The o-methoxyphenyl arsonic acid crystallized from
alcohol in beautiful white needles, m.p. 193°-194°.

Subs*. 0.2000, 0.1995 required 21.50, 21.46 cc. of 0.0808 N I.

Calc. for $C_7H_9O_4As$: As, 32.61%. Found: 32.57, 32.59%.
This acid is insoluble in cold water, soluble hot; slightly soluble
in cold alcohol, quite soluble hot; insoluble in ether and organic
solvents. It is readily soluble in aqueous alkalies, carbonates
and ammonia.

4-Methoxyphenyl Arsonic Acid: Michaelis[24] prepared this acid by
the hydrolysis of p-anisyl arsenic chloride, and Bertheim[25] ob-
tained it by the methylation of phenol p-arsonic acid. It may be
readily prepared from p-anisidine by Bart's reaction, and was ob-
tained in 35% yield from technical p-anisidine. It was crystallized
from water and was found to melt from 176°-177°. Bertheim reports
179°-180°.

6-Methyl-2-Nitrophenyl Arsonic Acid[22]: The nitro-toluidines used
for the preparation of the corresponding nitrotolyl arsonic acids
were prepared through the nitration of o-acetotoluide[26], and
separation of the isomeric nitro-acetotoluides by the Witt-Utermann
method. The method of Reverdin[27] and Crepieux was tried for this
separation but was found to be less satisfactory.

$30\frac{1}{2}$ g. of 3-nitro-o-toluidine, CH_3:1:NH_2:2, was diazo-
tized and treated with sodium arsenite in the usual way. The fil-
trate after acidification with acetic acid was concentrated, and

* All analyses for arsenic are by the method of
Robertson[43], unless otherwise stated.

filtered from the yellow flocculent by-product. This clear fil-
trate on cooling deposited a crop of pale yellow needles. A
sample of the latter was collected, washed with alcohol and
examined. It was found to be the mono-sodium salt of the nitro-
tolyl arsonic acid:

Subs. 0.2197 g. required 17.13 cc. of 0.0893 N I.

Calc. for $C_7H_7O_5NAsNa$: As = 26.50%   Found:

for $C_7H_6O_5NAsNa$: As = 24.58% As = 26.15%

This salt is moderately soluble in cold water, quite soluble hot;
it is very slightly soluble in alcohol and ether. The crystals
which separated were redissolved by heating and dilute hydrochloric
acid added to acid reaction to Congo paper. The 6-methyl-2-nitro-
phenyl arsonic acid separated in white flocks and weighed 40 g.
or 75% of the theoretical amount.

6-Methyl-4-Nitrophenyl Arsonic Acid[22]: From $30\frac{1}{2}$ g. of 5-nitro-o-
toluidine there was obtained 25-26 g. of this arsonic acid, in
pale yellow flocks. This is only 50% of the theoretical yield,
the difficulty in this case apparently being incomplete diazoti-
zation of the amine.

2-Methoxy-4-Nitrophenyl Arsonic Acid: The p-nitro-o-anisidine,
$NO_2,4;OCH_3,2;NH_2,1$; used for this synthesis was prepared through
the nitration of o-acetaniside and separation of the resulting
mixture of m- and p-nitro derivatives[28]. 123 g. of pure o-anisi-
dine, b.p. 99°-102° at 8-9 mm., was heated to boiling with 105 g.
of acetic anhydride and 33 cc. of glacial acetic acid. The solu-
tion was placed in a $1\frac{1}{2}$ l. flask provided with a good mechanical

stirrer and rapidly cooled by immersion in a freezing mixture. A solution of 65 cc. of fuming nitric acid, 1.52, in 90 cc. of <u>cold</u> acetic anhydride was added during the course of four hours, keeping the temperature below 0°. After the addition of the nitric acid was completed the mixture was allowed to warm up slowly to room temperature and stand for 36 hours. The red-brown solution was then poured into a mixture of 1300 g. of ice and water and a yellow precipitate of the mixed m- and p-nitro-acetanisides resulted. This was filtered with suction, washed thoroughly with water, and dried in the air. The yield was 208 g., which is almost the theoretical amount.

The crude reaction product was hydrolysed by warming on the water bath with a mixture of 350 cc. of concentrated sulfuric acid and 650 cc. of water. With occasional shaking the material dissolved and after $1-1\frac{1}{2}$ hours the solution was poured into a beaker to cool. The solution was then chilled, and the resulting paste of the sulfate of p-nitro-o-anisidine was filtered with suction and pressed as dry as possible. Without washing, the precipitate was transferred to a beaker and thoroughly mixed with cold water. This caused the hydrolysis of the gray sulfate to the free base. The bright yellow base, $NO_2\langle\hspace{1em}\rangle NH_2$ (with OCH_3) was filtered with suction and dried; m.p. $136^{\circ}-139^{\circ}$ (recorded in the literature, m.p. 140°).

The yield was 102 g. or 60% based on the anisidine used, and for ordinary purposes the crude product is sufficiently pure. Impure m-nitro-o-anisidine, $NO_2\langle\hspace{1em}\rangle OCH_3$ (with NH_2) was obtained on neutralization of the sulfuric acid filtrate with ammonia; the

amount was 55 g. or 32% based on the anisidine. It was found that the above procedure, whereby the acet-o-aniside was not isolated gave an increase of 5-10% of the product.

$33\frac{1}{2}$ g. of finely pulverised p-nitro-o-anisidine was suspended in hydrochloric acid, diazotized and treated with sodium arsenite in the customary way. The p-nitro-o-methoxy phenyl arsonic acid separated in small pale yellow needles and the yields were 30-32 g., which is 54-58% of the theoretical amount. This arsonic acid is very slightly soluble in cold water, more soluble hot; it is soluble to the extent of 6 g. per 100 cc. in boiling 90% alcohol, and crystallized on cooling in aggregates of long pale yellow needles; it is insoluble in ether and organic solvents; readily soluble in aqueous alkalies and ammonia. It does not melt up to 250°.

Subs. 0.1987, 0.2060 required 17.56, 18.27 cc. of 0.0808 N I.

Calc. for $C_7H_8O_6NAs$: As = 27.08%; Found: As - 26.78%, 26.86%.

The Preparation of Aminoaryl Arsonic Acids

There are two general methods of preparing the amino-aryl arsonic acids:first, the reduction of nitroaryl arsonic acids, and second, the direct arsenation of aryl amines. The first method is very general in its application and has led to the synthesis of a large number of amino arsonic acids, especially o- and m- derivatives. The second method is of limited application and is used chiefly for the preparation of p-aminoaryl arsonic acids.

The Reduction of Nitroaryl Arsonic Acids [22].

The reagents which have been used for the selective reduction of these acids are ammonium sulfide, sodium hydrosulfite, sodium amalgam, iron powder and alkaline ferrous hydroxide. The last was used by Benda[29], and by Jacobs, Heidelberger and Rolf. A modification of the method of the latter authors has proved quite satisfactory. The substitution of ferrous chloride for the sulfate is of considerable advantage, since this obviates the troublesome precipitation and filtration of barium sulfate.

General Procedure: A solution of ferrous chloride was prepared by treating an excess of powdered iron with hydrochloric acid and heating on a hot plate until no more gas was evolved. This solution was kept over metallic iron until just before using, and after filtration its ferrous chloride content was determined by permanganate titration.

A solution containing 7 equivalents of ferrous chloride was placed in a large wide mouth bottle fitted with a rubber stopper, and after thorough chilling by the addition of ice, a cold 20% solution of sodium hydroxide, 14 equivalents, was added. In the meantime a solution of the di-sodium salt of the nitro acid was prepared by dissolving 1 equivalent of the nitroaryl arsonic acid in 1000 cc. of 2-N sodium hydroxide. The solution of the nitro compound was added at once to the pale green jelly of ferrous hydroxide, and the bottle stoppered and vigorously shaken for 10-15 minutes. The color of the mixture changed from green to brown and after standing a short while with occasional shaking the mass was filtered with suction on a large funnel. The paste of

ferric hydroxide was sucked as dry as possible and then discarded.

The alkaline filtrate was concentrated on the steam bath to a volume of 700-750 cc., filtered from sodium chloride and the filtrate further concentrated in vacuo, 20 mm. When the volume is quite small the solution was treated with decolorizing charcoal, filtered and cooled. Dilute hydrochloric acid was then carefully added to the cold solution until it just reacted acid to Congo paper, and the amino arsonic acid precipitated. The products usually had a yellow-pink color and were purified by crystallization from water.

2-Aminophenyl Arsonic Acid, o-Arsanilic Acid[22]: Using 40 g. of o-nitrophenyl arsonic acid and following the directions outlined, 34 g. of o-arsanilic acid separated in slightly pink crystals, m.p. 150°-153°. This is 70% of the theoretical amount, and is slightly less than the yield obtained by Jacobs, Heidelberger and Rolf, but their results could not be duplicated in this laboratory.

2-Methyl-6-Aminophenyl Arsonic Acid[22]: The reduction of 26 g. of 2-methyl-6-nitrophenyl arsonic acid gave 12 g. of crude amino arsonic acid. This material was crystallized from water and melted from 173°-175°. The yields were 50-55% of the theoretical.

2-Methyl-4-Aminophenyl Arsonic Acid[22]: From 26 g. of the nitro acid by the usual method of reduction were obtained 12-15 g. of the crude amino arsonic acid, m.p. 216°-220°. This is 50-60% of the theoretical amount.

<u>2-Methoxy-4-Aminophenyl Arsonic Acid</u>: Derivatives related to this substance have been prepared by the arsenation of carbethoxy m-aminophenol,[42] and by the use of 5-nitro-2-aminophenol in the Bart reaction. The methyl ether can be most conveniently prepared by the reduction of 2-methoxy-4-nitrophenyl arsonic acid, obtained through the Bart reaction.

28 g. of the nitro arsonic acid was dissolved in 200 cc. of N-sodium hydroxide, and reduced in the usual way with ferrous hydroxide. The impure material was obtained as a brown crystalline precipitate amounting to 13-16 g. or 50-60% of the theoretical yield. The 2-methoxy-4-aminophenyl arsonic acid was crystallized from water, and was obtained in beautiful white needles.

Subs. 0.1503, 0.2000 g. required 15.07, 20.32 cc. of 0.0808 N I

Calc. for $C_7H_{10}O_4NAs$: As=30.36%. Found: 30.38%, 30.65%.

This acid is slightly soluble in cold water, more soluble hot; almost insoluble in alcohol, ether and organic solvents. It dis-solves readily in alkalies, carbonates, and ammonia, and in mineral acids. When heated rapidly it melts at 208°-209°; heated slowly it melts from 203°-204°.

Preparation by Direct Arsenation

<u>3-Methyl-4-Aminophenyl Arsonic Acid</u>: This acid is readily prepared by the Bechamp reaction from o-toluidine[30] and arsenic acid. The method used was a modification by W. Lee Lewis for the preparation of arsanilic acid. The crude o-toluidine arsonic acid, which was slightly pink in color, was purified by precipitating the mono-sodium salt from its aqueous solution by pouring into absolute

alcohol. It separated in large white crystals, containing 3 H_2O,
and not $3\frac{1}{2}$ H_2O as stated by Pyman:

Subs. 0.9700, 1.2576 g. heated at 120° lost 0.1718, 0.2215 g

Calc. for $C_7H_8O_3NNa$, $3H_2O$: 17.59%   Found: 17.72%.

$C_7H_8O_3NNa$, $3\frac{1}{2}H_2O$: 19.94%   17.62%.

The free acid was obtained on adding the calculated quantity of
hydrochloric acid to a solution of the sodium salt. It separated
in white leaflets or plates, m.p. 195°-198°.

3-Bromo-4-Aminophenyl Arsonic Acid: Although the halogenated
anilines may be used in the Bechamp reaction, it is usually more
convenient to prepare the halogenated aminoaryl arsonic acids by
indirect means. Bertheim[31] obtained mono-bromoarsanilic acid by
the direct bromination of arsanilic acid with half the theoretical
amount of bromine.

110 g. of arsanilic acid, ($\frac{1}{2}$ mole) was dissolved in
2000 cc. of hot glacial acetic acid and the solution quickly
chilled to room temperature. A solution of 40 g. of bromine
($\frac{1}{4}$ mole) in glacial acetic acid was then added with good stirring
during the course of 4-5 hours. The product was isolated accord-
ing to the procedure of Bertheim, and the monobromo arsanilic acid
separated in white leaflets weighing 52 g. or 70% of the theor-
etical amount. The yield stated by Bertheim was 47% and the im-
provement was probably due to the very slow addition of the
bromine, good stirring and the use of a slightly larger amount of
solvent.

B. The Condensation of Arylamino Arsonic Acids with Pyruvic Acid
and Aldehydes.

Arsanilic Acid, Pyruvic Acid and Benzaldehyde[41]: A mixture of 21.7
g. of arsanilic acid (1 mole), 10.6 g. of benzaldehyde (1 mole)
and 200 cc. of absolute alcohol was heated to boiling under reflux
on a steam bath. After a short while most of the arsanilic acid
passed into solution and 8.8 g. of pyruvic acid (1 mole) were
added. The solution was then heated to boiling for $3\frac{1}{2}$-4 hours
and then filtered hot to remove a slight amount of insoluble mater-
ial. On cooling the filtrate a yellow precipitate resulted which
was filtered, washed sparingly with alcohol, finally with ether
and then dried in vacuo. The crude condensation product thus ob-
tained was pale yellow in color and melted with complete decomposi-
tion at $180°$-$183°$. After one crystallization from ordinary alcohol
and washing with alcohol followed by ether, the substance is pure
and is then a cream colored powder which starts to darken at
about $180°$, and melts with decomposition at $186°$-$187°$ (cor.) The
yields of crude product varied from 18-24 g. which is 50-65% of
the theoretical amount. After repeated crystallization from
alcohol the substance was obtained in pure white leaflets.

The arsenic was determined by Ewins' method, the
nitrogen by the Kjeldahl method, and the carbon by the Parr total
carbon method:

Subs. 0.5001, 0.5005 g., CO_2, 563.5 cc. $(28.5°, 746$ mm$)$
565.3 cc. $(30.5°, 746$ mm$)$

0.1999, 0.2023 g. required 14.46, 14.49 cc. 0.0736 N I.

0.5001, 0.5034 g. 18.32, 18.36 cc. 0.0699 N HCl.

Calc. for $C_{16}H_{14}O_5NAs$: C, 51.20%; As, 20.00%; N, 3.73%.

Found: C, 51.54, 51.20%; As, 19.97, 19.77%; N, 3.58, 3.57%. This substance is slightly soluble in water; more soluble in cold methyl and ethyl alcohol and glacial acetic acid, very soluble in these solvents hot; insoluble in ether and organic solvents. It is readily soluble in alkali hydroxides and carbonates, and in ammonia; insoluble in dilute mineral acids in the cold, decomposed on warming.

When the crude material was recrystallized from alcohol a certain amount of insoluble material remained, which consisted in part of benzylidene arsanilic acid. The latter was isolated by boiling the residue with a large volume of absolute alcohol and allowing the filtrate to cool and concentrate. The benzylidene arsanilic[32] acid separated in white heavy granular crystals, readily soluble in alkalies, and decomposing on heating to 225°.

Subs. 0.2078, 0.2100 g. required 15.27, 15.42 cc. 0.0893 N I.

Calc. for $C_{13}H_{12}O_3NAs$: As, 24.59%. Found: As, 24.60%, 24.62%. In addition to the benzylidene arsanilic acid a less soluble substance remained in the insoluble portion.

A number of experiments were made to determine the best conditions for carrying out the reaction and it was finally decided that the use of mechanical stirring and a temperature of 65°-70° are the most favorable conditions. It was found that only half of the alcohol was essential to carry out the reaction and obtain complete solution of the products, but the mass becomes so solid on cooling that it is advisable to use the larger quantity.

It was found that ethyl alcohol could be replaced by methyl, and the condensation effected in the usual manner[33]. It is unnecessary to use absolute alcohol for the solvent, and fair results were obtained by the use of 95% and 90% alcohol. In these cases, however, the yields were not so good and the product was more highly colored.

The same product resulted from the use of ethyl pyruvate[34] instead of pyruvic acid, under the same conditions. 11.6 g. of ethyl pyruvate was substituted for 8.8 g. of pyruvic acid in the above directions. The product was isolated in the usual manner but the yield was poorer than when pyruvic acid was used. The product after recrystallization from absolute alcohol melted from 185°-187°, w. dec., and a mixed melting point with the first condensation product was not lowered.

Subs. 0.2074 g. required 12.42 cc. of 0.0893 N I.

Calc. for $C_{16}H_{14}O_5NAs$: As = 20.00%. Found: 20.06%.

The condensation was also carried out in ether, but in this case the reaction was incomplete, due to the insolubility of the arsanilic acid. A mixture of 10.6 g. of benzaldehyde and 8.5 g. of pyruvic acid was added to 21.7 g. of arsanilic acid covered with 350 cc. of ether. The mixture was stirred vigorously for 40 hours and at the end of this time a flocculent precipitate had formed in the ether. This was separated by decantation from the heavy granular crystals of unused arsanilic acid and then filtered from the ether. The material weighed 20 g. and was much darker yellow in color than the ordinary crude condensation product. After two crystallizations from alcohol the material was obtained in white leaflets, m.p. 185°-187°, w. dec, and was

proved to be identical with the first condensation product by
mixed melting points and analysis:

Subs. 0.1516 g. required 9.10 cc. of 0.0893 N I.

Calc. for $C_{16}H_{14}O_5NAs$: As, 20.00%. Found: 20.10%.

The reaction between arsanilic acid, pyruvic acid and substituted
aldehydes was carried out according to the directions given for
benzaldehyde, using each one of the constituents in equimolar
proportions.

Salicylaldehyde: This aldehyde gave an orange red solution from
which a product separated on concentration. This was more highly
colored than that from benzaldehyde, and it rapidly darkened on
exposure to the air. No suitable method of purification was found.

2-Methoxy benzaldehyde: Using the methyl ether[35] of salicyl alde-
hyde instead of the free phenol, a good yield of the condensation
product was obtained. The material after crystallization from
alcohol, was obtained as a pale yellow powder, m.p. 173°-176°, w.dec.

Subs. 0.2025, 0.2022 required 12.61, 12.25 cc. 0.0808 N I.

Calc. for $C_{17}H_{16}O_6NAs$: As, 18.56%. Found: 18.87%, 18.36%.

4-Methoxy benzaldehyde: Anisaldehyde gave a product which after
crystallization from alcohol was almost white; m.p. 164°-165°, w.dec.

Subs. 0.2005, 0.2000 g. required 10.38, 10.51 cc. 0.0954 N I.

Calc. for $C_{17}H_{16}O_6NAs$: As, 18.56%. Found: 18.53%, 18.63%.

4-Dimethylamino benzaldehyde: When the pyruvic acid was added to
a mixture of arsanilic acid and dimethylamino benzaldehyde[36], a
deep red color was formed which became darker during the heating.

The product separated as a dark red powder, which was purified
with difficulty from alcohol.

3,4-Methylenedioxy benzaldehyde: Piperonal was found to give a
good yield of the condensation product, which after crystalliza-
tion from alcohol was obtained as a light yellow powder, m.p.
176°-178° w. dec.

   Subs. 0.1474 g. required 7.80 cc. 0.0893 N I.

   Calc. for $C_{17}H_{14}O_7NAs$: As, 17.90%. Found: 17.73%.

4-Chlorobenzaldehyde : This aldehyde gave satisfactory yields of
a product which after two crystallizations from alcohol was ob-
tained as a white powder, m.p. 163°-165°, w. dec.

   Subs. 0.2505 g. required 14.90 cc. of 0.0808 N I.

   Calc. for $C_{16}H_{13}O_5NClAs$: As, 18.29%. Found: 18.00%.

Cinnamic Aldehyde: This aldehyde seemed to react with the arsan-
ilic acid and pyruvic acid, but only a colored impure condensation
product was obtained, and no method was found for its purification.

Paraldehyde: In place of 103 g. of benzaldehyde, 4.4 g. of paralde-
hyde was used and in this case no condensation product separated
from the cooled solution. On allowing $\frac{3}{4}$ of the alcohol to evapor-
ate, 18 g. of a yellow solid remained. A portion of this was
crystallized from water and proved to be impure arsanilic acid:

   Subs. 0.2001, 0.1996 g. required 24.50, 24.13 cc. 0.0736 N I.

   Calc. for $C_{11}H_{12}O_5NAs$: As, 23.96%.   Found:

         $C_{17}H_{18}O_7N_2As_2$: As, 29.30%   33.79

         Arsanilic Acid: 34.56%   33.35%

n-Butyraldehyde was also tried, but no condensation product was obtained.

3-Aminophenyl Arsonic Acid, Pyruvic Acid and Benzaldehyde: In contrast to the p-compound, o-arsanilic acid is quite soluble in alcohol. To carry out the reaction the o-arsanilic acid was dissolved in the hot alcohol, and the benzaldehyde and pyruvic acid added to the hot solution. A crystalline precipitate was formed, but on heating for $1-1\frac{1}{2}$ hours at 70° this redissolved. On filtering and cooling the reaction mixture to 20° no precipitate formed, but on concentrating and cooling to -10° a yellow precipitate resulted. This was analysed and found to be the benzylidene derivative of o-arsanilic acid, m.p. $237^{\circ}-239^{\circ}$.

From a similar experiment the crystalline precipitate obtained at first was filtered and washed with alcohol and ether. It is a heavy granular material, m.p. $226^{\circ}-228^{\circ}$, with previous darkening. Analysis indicated that it was benzylidene o-arsanilic acid, $C_6H_5CH=N.C_6H_4.AsO_3H_2$:

Subs. 0.1997 required 14.70 cc. 0.0893 N I.

Calc. for $C_{13}H_{12}O_3NAs$: As, 34.58%. Found: 34.66%.

The filtrate from the crystalline precipitate on cooling deposited an additional amount of material, almost white in color. This was filtered, washed with alcohol and ether, and found to melt from $225^{\circ}-228^{\circ}$. This indicated that it was benzylidene o-arsanilic acid, and was confirmed by analysis:

Subs. 0.1985 g. required 14.65 cc. 0.0893 N I.

Calc. for $C_{13}H_{12}O_3N$ As: 34.58%. Found: 34.74%.

For comparison a sample of benzylidene o-arsanilic acid was pre-
pared by heating o-arsanilic acid with one mole of benzaldehyde
in alcoholic solution. The product crystallized out in granules,
m.p. 228°-230°, and was identical with the above compounds.

3-Methyl-4-Aminophenyl Arsonic Acid, Pyruvic Acid and Benzaldehyde:
Methyl arsanilic acid was treated with benzaldehyde and pyruvic
acid in the usual way and no condensation product separated. On
evaporating $\frac{1}{2}$ of the alcohol and cooling, a product separated
which was filtered and washed with alcohol and ether. This was
recrystallized from alcohol and obtained as a cream colored
powder, m.p. 202°-205°, w. dec. The analysis indicated that it
was the benzylidene derivative:

Subs. 0.2001, 0.2000 g. required 13.80, 13.90 cc.0.0893 N I.

Calc. for $C_{14}H_{14}O_3NAs$: As, 23.51%. Found: 23.10%, 23.28%.
The reaction was repeated with longer heating, but the same
product was obtained.

4-Chlorobenzaldehyde: Using p-chlorobenzaldehyde in place of benz-
aldehyde, a yellow precipitate was obtained from the reaction
mixture on cooling. This was crystallized from alcohol and ob-
tained as a pale yellow powder, m.p. 255°-260°, w. dec. The
analysis indicated that this was the benzylidene derivative and
that the pyruvic acid had not taken part in the condensation:

Subs. 0.2018, 0.2001 required 13.74, 13.31 cc. 0.0808 N I.

Calc. for $C_{14}H_{13}O_3NClAs$: As, 21.20%.

2-Nitrobenzaldehyde: From this reaction a product was obtained

which was purified with difficulty from alcohol. Analysis in-
dicated that it was a mixture of arsanilic acid, and a small amount
of other material:

  subs. 0.2002 g. required 17.98 cc. 0.0893 N I.

  Calc. for arsanilic acid, As 34.56%. Found: 30.1%.

3-Bromo-4-Aminophenyl Arsonic Acid, Pyruvic Acid and Benzaldehyde:
When bromo-arsanilic acid was used in place of arsanilic acid it
was very difficult to isolate any product from the reaction mixture.
On concentrating to a small volume, a precipitate was obtained which
was purified with difficulty from alcohol. This substance proved
to be chiefly unchanged bromo-arsanilic acid, probably contaminated
with some of the benzylidene derivative:

  Subs. 0.2334 g. required 16.07 cc. 0.0893 N I

  Calc. for Bromoarsanilic acid, As, 25.33%.

        Benzylidene derivative, As, 19.53%

   Found: As, 23.16%.

2-Methyl-4-Aminophenyl Arsonic Acid, Pyruvic Acid and Benzaldehyde:
A suspension of the arsonic acid in absolute alcohol was treated
with benzaldehyde and pyruvic acid, and vigorously stirred under
reflux at 70°. The acid gradually passed into solution and after
3-3$\frac{1}{2}$ hours heating the reaction mixture was filtered and cooled.
The condensation product separated in good yield and after washing
with alcohol and ether remained as a cream colored powder decompos-
ing on heating from 180°-186°.

  Subs. 0.1981, 0.2003 g. required 11.32, 11.55 cc. 0.0893 N I.

   Calc. for $C_{17}H_{16}O_5NAs$: As, 19.27%. Found: 19.14%, 19.27%.

3-Methoxy-4-Aminophenyl Arsonic Acid, Pyruvic Acid and Benzaldehyde:
Using the same method as in the preceding example, the condensa-
tion product was obtained as a yellow powder decomposing on heating
to 175°-180°, with previous darkening.

Subs. 0.1472 g. required 7.79 cc. 0.0893 N I.

Calc. for $C_{17}H_{16}O_6NAs$: As, 18.56%. Found: 17.73%.

Condensation of an Aminoaryl Arsinic Acid: An arsinic acid derived
from p-arsanilic acid was available and this was treated with
pyruvic acid and benzaldehyde in the usual manner. From p-amino-
phenyl arsinic (acid) acetanilide[*], $p-NH_2C_6H_4AsO_2H.CH_2CONHC_6H_5$, a
yellow solid was obtained decomposing at 173°-175°.

C. Reactions of the Condensation Products.

For studying the structure of the condensation products
the substance was used that was obtained by heating p-arsanilic
acid, benzaldehyde and pyruvic acid in absolute alcoholic solution.
The material was recrystallized from alcohol and was obtained as a
cream colored powder melting with decomposition from 185°-187°,
with previous darkening.

Decomposition on Heating: A qualitative experiment showed that the
material evolved carbon dioxide on heating to its decomposition
temperature, and in order to obtain definite information the ex-
periment was carried out quantitatively. A weighed sample was
suspended in ethyl benzoate, heated to boiling for 20 minutes, and
the carbon dioxide in the gas evolved was determined by difference
after absorption in potassium hydroxide.

[*] Prepared by the action of chloroacetanilide upon
sodium phenyl arsenite. Reference 38.

Subs. 1.000 g. gave 58.5 cc. CO_2, 24° and 743 mm.

Converted to standard conditions .... 52.5 cc.

Calculated for one mole CO_2.............. 60.0 cc.

These date indicated that the amount of carbon dioxide formed corresponded roughly to one mole.

This reaction was first considered to be evidence of the cinchoninic acid formula for the product, but in order to be sure of the conclusion it was decided to try an experiment with a known diketopyrrolidine. For this purpose the compound prepared by Borsche[16] from p-nitraniline, pyruvic acid and benzaldehyde in alcoholic solution was used. On repeating Borsche's work the compound was obtained as a yellow powder, m.p. 182°-183°, after repeated crystallization from glacial acetic acid.

The decomposition was carried out exactly as in the preceding case:

Subs. 1.042 g. gave 54.2 cc. CO_2, 25° and 755 mm.

Converted to standard conditions .... 49.3 cc.

Calculated for one mole CO_2.............. 78.8 cc.

Found: 63% of one mole.

Since it was thought that the presence of an arsonic acid grouping might affect the decomposition, a similar experiment was carried out in which 2 g. of o-nitrophenyl arsonic acid was added to the material before heating.
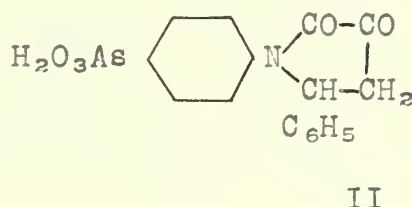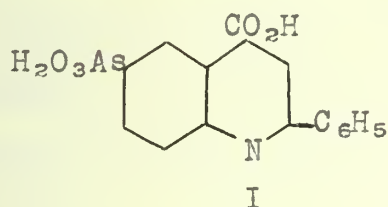
Subs. 1.118 g. gave 89.4 cc. CO_2, 28° and 755 mm.

Converted to standard conditions .... 80.7 cc.

Calculated for one mole CO_2.............. 84.7 cc.

Found: 95% of one mole.

These results were altogether unexpected since it is not easy to explain the formation of a mole of carbon dioxide on the decomposition of a diketopyrrolidine derivative.

This indicated that the formation of carbon dioxide on decomposing the condensation product could not be taken as evidence for distinguishing between these formulae, providing the compound obtained from p-nitraniline is a true diketopyrrolidine derivative, as it is formulated by Borsche to be.

On boiling the condensation product with mineral acids, a heavy viscous oil is formed which sinks to the bottom of the container and on cooling sets to a brittle mass. An attempt was made to esterify the substance by treating with dry hydrochloric acid in alcoholic solution, but the acid caused decomposition of the condensation product.

Fusion with sodium hydroxide: The fusion of phenyl arsonic acid with alkalies was carried out by La Coste [37], who states that it gives with potassium hydroxide $\frac{1}{4}$ phenol and $\frac{3}{4}$ benzene, but with sodium hydroxide chiefly benzene. It thus appeared that by fusion of the condensation product with sodium hydroxide an arsenic free substance would be obtained that could easily be identified. To test out the reaction two preliminary experiments were run:

a. 25 g. of phenyl arsonic acid was mixed thoroughly with five times its weight of sodium hydroxide and distilled from

ammonium salt may be prepared.[33] The behavior on treating with
sodium hydroxide is rather unusual:

The material dissolved readily in one mole of aqueous
sodium hydroxide to a clear yellow solution which was filtered and
allowed to stand at room temperature. After a short while the
solution became turbid, and deposited a white precipitate. A
strong odor of benzaldehyde was noticed. After 24 hours the pre-
cipitate was filtered and examined. It contained arsenic and was
soluble in alkalies; it was purified with difficulty from alcohol
and obtained as a white powder melting with decomposition from
140°-150°.

On treating the condensation product with two or more
moles of sodium hydroxide a clear yellow solution resulted which
remained perfectly clear for an indefinite period. A few tests
were made to determine in a rough way the P_H values of solutions
of the condensation product in various quantities of alkali. The
Clark-Lubs series of indicators was used:

	Sodium Hydroxide	P_H value	Notes
a.	1 mole	approx 3.0	deposits white precipitate
b.	$1\frac{1}{2}$ moles	3.5 - 4.4	deposits white precipitate not as much as in a.
c.	2 moles	7.2 - 8.0	clear yellow solution
d.	$2\frac{1}{2}$ moles	approx 8.8	clear yellow solution
e.	3 moles	8.8 - 9.6	solution darker than c.

From a solution of the condensation product in two
moles of alkali, copper sulfate precipitates a green salt; silver,
lead, mercurous, mercuric, cadmium nitrates light yellow salts and
cobalt and ferric nitrates red-brown salts.

a copper flask. From the distillate there was obtained 5 g. of

benzene, water and a small amount of a crystalline substance,

presumably diphenyl.

b. 25 g. of arsanilic acid was fused with sodium

hydroxide under the same conditions and gave 7 g. of aniline.

c. 30 g. of the condensation product on fusion with

150 g. of sodium hydroxide gave a distillate which consisted of a

red oily substance and water. This was treated as indicated:

Acidified with dilute hydrochloric
acid and extracted with ether:

Ether Extract: Hydrochloric Acid Extract:

Dried over calcium   Treated with sodium hydroxide,gave

cloride,and then   a red-brown oil;taken up in ether,

distilled: dried and distilled:

a. 2-3 cc.b.p.120-150°   a. 4-5 cc.175-185°   b. few drops of

probably phenyl   identified as anil-   a very high-boil

ethylene.   ine,by conversion   ing base,which

                            to acetanilid.   decomposes on

                                                    distilling!.

The formation of aniline from the condensation product indicated

that it was not the phenyl cinchoninic acid derivative , since

this would yield phenyl quinoline, but it does not help to distin-

guish between the formulae II and V:
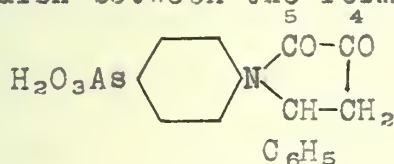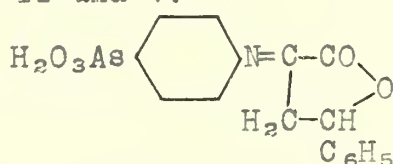
II.   V.

Treatment with aqueous alkalies: The condensation product is

readily soluble in caustic alkalies, carbonates, and ammonia. By

passing dry ammonia into a solution in absolute alcohol, a mono-

An attempt was made to isolate a sodium salt by pour-
ing an aqueous solution of the mono-sodium salt into absolute
alcohol. A white precipitate resulted which was filtered and
washed with dry ether. An analysis indicated that this was the
di-sodium salt of arsanilic acid:

Subs. 0.1830, 0.2105 required 15.36, 17.70 cc. 0.0893 N I.

Calc. for $C_6H_6O_3NAsNa_2$: As, 28.73%. Found: 28.07%, 38.17%.

This salt forms very hygroscopic white crystals which dissolve
readily in water to a clear solution. It does not appear to have
been described in the literature.

Treatment with aniline: With the idea of obtaining an anil from the
4-keto group in the formula II, a solution of 19 g. (1 mole) of the
condensation product in 100 cc. of hot absolute alcohol was treated
with 4.5 g. (1 mole) of aniline. The solution turned red in color
and was heated for $\frac{1}{2}$-$\frac{3}{4}$ hour. On cooling a precipitate formed which
was filtered, washed with ether and examined. It was found that a
considerable portion of the material was insoluble in boiling 10%
sodium hydroxide, and therefore did not contain the arsonic acid
grouping. This material was filtered and investigated. It melted
with decomposition from 147°-148° and was thought to be identical
with the compound m.p. 147°-148° obtained by Schiff[21] and by
Garzarolli-Thurnlackh[17] on treating benzylidene aniline in benzene
solution with pyruvic acid.

It was thought that by treating the condensation
product with an excess of aniline, the Döbner anil compound, m.p.
225° could be obtained, and an experiment was carried out as above
using $3\frac{1}{2}$ moles of aniline. On concentrating and cooling a precipi-

tate was obtained which was completely soluble in cold sodium hydroxide. On neutralizing the filtered alkaline solution, a precipitate was obtained which proved to be arsanilic acid. None of the compound melting at 225° could be isolated.

The regeneration of arsanilic acid on treatment with such a mild reagent as aniline seems to give evidence that formula V is more likely than II. Using formula V the reactions of the condensation product can be explained according to the following diagram:

IV. SUMMARY

The application of the Döbner cinchoninic acid synthesis to arsanilic acid, benzaldehyde, and pyruvic acid gave a condensation product of the composition: $C_{16}H_{14}O_5NAs$.

The reactions of this condensation product were studied and the following formulae proposed:

I   II
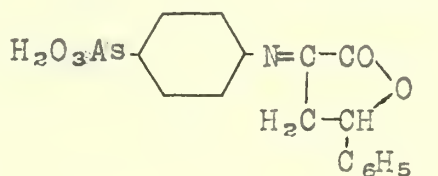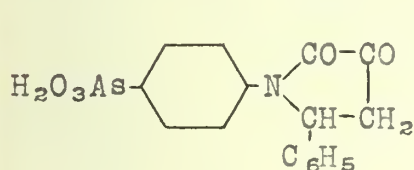
The structure of the product was not definitely established, but the evidence favors formula II.

By the use of various aldehydes and aminoaryl arsonic acids, the following generalizations were made concerning the limitations of this reaction:

i. Aminoaryl arsonic acids with substituents in the ortho position to the amino group form benzylidene derivatives which do not react further with pyruvic acid.

ii. The usual condensation products are obtained from compounds substituted in the meta position to the amino group.

iii. The reaction is general for aromatic aldehydes, but not for the simple aliphatic aldehydes.

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P A R T   T W O

BENZYL ARSONIC ACID

B E N Z Y L   A R S O N I C   A C I D

INTRODUCTION

This work on benzyl arsonic acid was undertaken with the object of obtaining new organic arsenic compounds which might prove of therapeutic value. Although a large number of derivatives of phenyl arsonic acid have been prepared in the last fifteen years, due to the stimulus of Ehrlich and Bertheim's work, there has been little development along the line of aliphatic arsonic acids. For our work benzyl arsonic acid seemed especially desirable, since it contained an aliphatic arsonic acid grouping, $-CH_2AsO_3H_2$, and in addition a phenyl group, by means of which it was hoped to introduce certain other physiologically active groupings into the molecule.

The only series of aliphatic arsenic compounds which has been thoroughly studied and applied in medicine, is the methyl series. Methyl arsonic acid and dimethyl arsinic acid, were until recently the most readily accessible arsenicals of the aliphatic series. These two substances are used therapeutically in the form of their salts, most commonly, disodium methyl arsonate (Arrhenal), and sodium cacodylate. Gautier[1] recommended the use of Arrhenal in therapeutics and stated that it has specific action on malaria; however, it does not possess trypanocidal properties. The latter fact is in keeping with recent work which has shown that nitrogen must be present in some form in order to produce specific trypanocidal substances.

Benzyl arsonic acid can be very easily prepared, and the problem was to study the properties of this substance with

the hope of preparing a derivative which would possess trypano-
cidal action and be of low toxicity. The relatively low toxicity
of the aliphatic arsenic acids in general, makes them very desir-
able as starting materials.

HISTORICAL PART

The first work on arsenic compounds of the benzyl
series was reported by Michaelis[2] and Paetow in 1885. From the
products of the interaction of benzyl chloride, arsenic trichlor-
ide, and metallic sodium in dry ether suspension, they obtained
dibenzylarsinic acid, tribenzyl arsine, and tribenzylarsine
oxide. From these substances a large number of more complex
substances were obtained, the most important of which were:

(a) Tribenzyl alkyl arsonium halides. These were made by
heating tribenzyl arsine with alkyl iodides at 100°.

(b) Tribenzyl methylarsonium hydroxide and tetrabenzyl
arsonium hydroxide[3]. These were made from the corres-
ponding iodides with silver oxide; they are very strong
bases and rapidly absorb carbon dioxide from the air.

(c) Benzyl arsenious chloride. This was made by heating
tribenzyl arsine with arsenic chloride; it is very un-
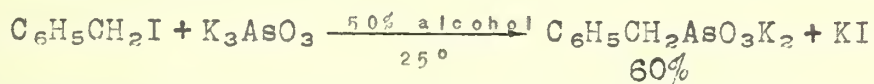stable and decomposes in the air:

$$C_6H_5CH_2AsCl_2 + O \longrightarrow C_6H_5CH_2Cl + AsOCl$$
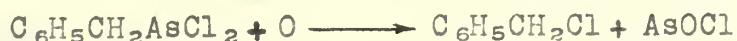
After this work, no important contribution to the
benzyl arsenic series was reported until Dehn[4] and McGrath in
1906 showed that the extension of Meyer's reaction to benzyl
iodide gave good yields of benzyl arsonic acid. They studied

the properties of this acid, and found that the arsenic was split off from the organic residue more readily than in other simple aliphatic and aromatic arsonic acids. Dehn[5] obtained benzyl arsine by the reduction of benzyl arsonic acid with amalgamated zinc dust and hydrochloric acid. By the treatment of benzyl magnesium chloride in ether solution with arsenic trioxide, Sachs and Kantorowicz[6] obtained a substance which they formulated as a hydrated dibenzyl arsenious acid, $(C_6H_5CH_2)_2AsOH \cdot H_2O$, but the constitution of this acid was not proved and needs verification.
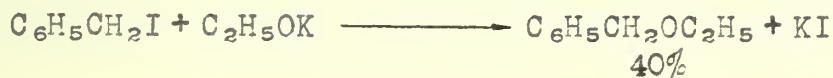
In 1915 shortly before his death, Bertheim[7] studied the mixed aromatic-aliphatic secondary arsinic acids, and obtained benzyl phenyl arsinic acid by treating sodium phenyl arsenite with benzyl chloride.

THEORETICAL PART

Since considerable quantities of benzyl arsonic acid
would be required for this work it was desired to find a conven-
ient method of preparing the substance. The method of Dehn and
McGrath is too unwieldy for the preparation of large quantities
of the substance and involves a considerable loss of material
due to a side reaction:

$$C_6H_5CH_2I + K_3AsO_3 \xrightarrow[25^\circ]{50\% \text{ alcohol}} C_6H_5CH_2AsO_3K_2 + KI$$
$$60\underline{\%}$$

Side reaction:

$$C_6H_5CH_2I + C_2H_5OK \longrightarrow C_6H_5CH_2OC_2H_5 + KI$$
$$40\%$$

By omitting the use of alcohol, and using a higher temperature
and vigorous mechanical stirring, benzyl arsonic acid was pre-
pared in good yields from benzyl chloride or bromide, and aqueous
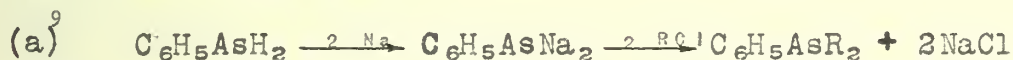sodium arsenite.

Benzyl arsonic acid was thus readily available at a
low cost, and seemed promising as a starting point for a number
of derivatives. By reduction, benzyl arsine is obtained, and it
seemed worth while to study this substance by trying to react it
with aldehydes to produce substances similar to those obtained
by Adams and Palmer[a]:

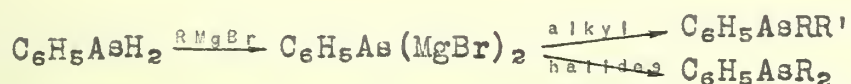$$C_6H_5AsH_2 + 2RCHO \longrightarrow C_6H_5As \begin{matrix} CHOH \cdot R \\ CHOH \cdot R \end{matrix}$$
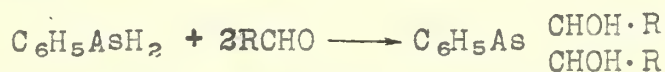
It was found that the reaction did not proceed as smoothly as
with phenyl arsine, and the chief products of the reaction were
benzyl arsonic acid and a red condensation product, (probably

identical with that obtained by Dehn from benzyl arsine), which
is presumably arseno-phenylmethane, $(C_6H_5CH_2As{=}AsCH_2C_6H_5)_2$.

Recent work in this laboratory has given two new
methods by which derivatives of the arsines may be prepared, and
these may prove to be useful in the case of benzyl arsine. The
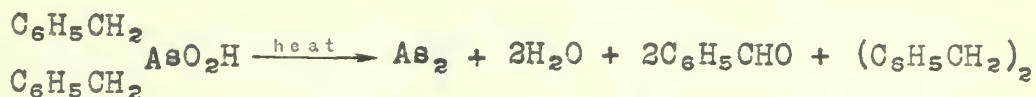reactions involved are:

(a)[9] $C_6H_5AsH_2 \xrightarrow{2\,Na} C_6H_5AsNa_2 \xrightarrow{2\,RCl} C_6H_5AsR_2 + 2NaCl$

(b)[10]

$C_6H_5AsH_2 \xrightarrow{RMgBr} C_6H_5As(MgBr)_2 \underset{\text{halides}}{\overset{\text{alkyl}}{\xrightarrow{\hspace{1cm}}}} \begin{array}{l} C_6H_5AsRR' \\ C_6H_5AsR_2 \end{array}$

It seems likely that a number of interesting derivatives could be
prepared from benzyl arsine by the application of these new re-
actions.

During the course of the work on the preparation and
properties of benzyl arsonic acid some interesting observations
were made on the products of its decomposition. It was noted that
in general the arsenic compounds of the benzyl series were very
easily broken down into inorganic derivatives of arsenious acid
and organic benzyl derivatives. Michaelis and Paetow observed
that on heating, dibenzyl arsinic acid was decomposed into
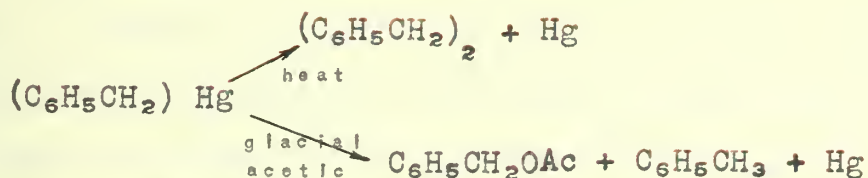arsenic, benzaldehyde and dibenzyl:

$$\begin{array}{l} C_6H_5CH_2 \\ AsO_2H \xrightarrow{heat} As_2 + 2H_2O + 2C_6H_5CHO + (C_6H_5CH_2)_2 \\ C_6H_5CH_2 \end{array}$$

By strong hydrochloric acid it is decomposed completely into
arsenic chloride, benzyl chloride and toluene:

$$(C_6H_5CH_2)_2\,AsO_2H + 4HCl = C_6H_5CH_2Cl + C_6H_5CH_3 + AsCl_3 + H_2O$$
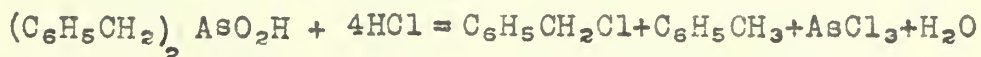
These reactions are somewhat similar to the decomposition[11] of

dibenzyl mercury:

$$(C_6H_5CH_2)_2 + Hg$$

$(C_6H_5CH_2)\ Hg$ $\xrightarrow{heat}$

$\xrightarrow[acetic]{glacial}\ C_6H_5CH_2OAc + C_6H_5CH_3 + Hg$

Michaelis and Paetow observed that the quaternary benzyl arsonium hydroxides on heating with alkalies gave toluene and a tertiary arsine oxide:

$$(C_6H_5CH_2)_4\ AsOH \xrightarrow{KOH} (C_6H_5CH_2)_3\ AsO + C_6H_5CH_3$$
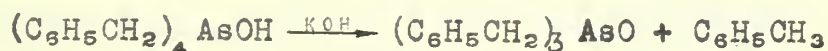
Benzyl arsenious chloride was also found to be extremely easily decomposed; with water it gives benzaldehyde and arsenic trioxide.

Dehn and McGrath showed that strong hydrochloric acid decomposed benzyl arsonic acid into benzyl chloride and arsenic trioxide:

$$2\ C_6H_5CH_2AsO_3H_2 + 2HCl \longrightarrow 2C_6H_5CH_2Cl + As_2O_3 + 3H_2O$$
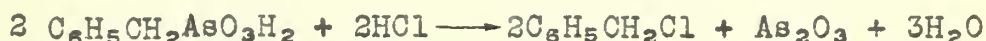
and Bertheim states that warm hydrochloric acid converts the secondary arsinic acid, benzyl phenyl arsinic acid, into benzyl chloride and phenyl arsenious chloride:

$$C_6H_5CH_2As{\overset{C_6H_5}{O_2H}} \xrightarrow{HCl} C_6H_5CH_2Cl + C_6H_5AsCl_2 + 2H_2O$$
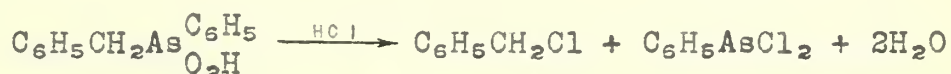
It was observed that the halogenated benzyl arsonic acids behaved in the same way, yielding the halogenated benzyl chlorides on treatment with strong hydrochloric acid with slight warming.

On heating slightly above its melting point, benzyl arsonic acid is decomposed into arsenic trioxide and a liquid product. The liquid was investigated by Dehn and McGrath and stated to consist of benzyl alcohol, benzaldehyde, stilbene and water. They give as the most important reaction:

$$2\ C_6H_5CH_2AsO_3H_2 \longrightarrow C_6H_5CH_2OH + C_6H_5CHO + As_2O_3 + 3H_2O$$
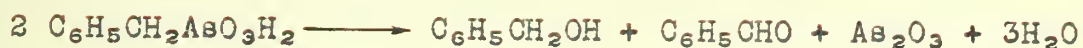
It will be noted on careful observation that this equation does not balance; the products of the reaction have two hydrogens and two oxygens in excess of the starting materials.

On carefully decomposing a large quantity of benzyl arsonic acid the chief reaction was observed to be:

$$3\ C_6H_5CH_2AsO_3H_2 \xrightarrow{heat} 3C_6H_5CH_2OH + As_2O_3 + H_2O$$
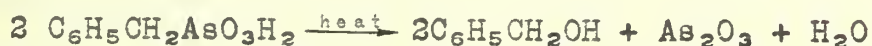
No benzaldehyde was found in the liquid product obtained from two hundred grams of benzyl arsonic acid, but a high boiling material was obtained which was shown to be dibenzyl ether. This may be accounted for by the following equation:

$$2\ C_6H_5CH_2AsO_3H_2 \xrightarrow{heat} (C_6H_5CH_2)_2O + As_2O_3 + 2H_2O$$
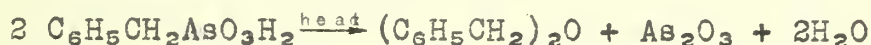
or possibly by a secondary reaction whereby a part of the benzyl alcohol formed is dehydrated under the influence of unchanged benzyl arsonic acid in the reaction mixture. The high boiling material obtained by Dehn and McGrath was shown to be dibenzyl ether, and not a mixture of benzyl alcohol and stilbene as they considered it to be.

By decomposing benzyl arsonic acid under vigorous heating it was noted that benzaldehyde was obtained among the decomposition products, along with an ill-smelling gas. From these considerations it seemed likely that benzaldehyde is not one of the main products of the reaction, but is formed by a side reaction:

$$3\ C_6H_5CH_2AsO_3H_2 \xrightarrow{heat} 3C_6H_5CHO + As_2O_3 + AsH_3 + 3H_2O$$
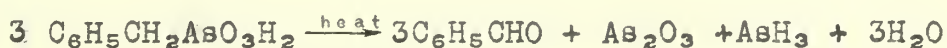
The decomposition strongly of benzyl arsonic acid by mineral acids, such as hydrochloric and sulfuric, is quite complete at

elevated temperatures, and it was found that this procedure could be used to determine benzyl arsonic acid quantitatively. The ease of preparing very pure benzyl arsonic acid has led to the use of the latter as a standard for determining the titre of iodine solutions, and very good results have been obtained.

In determining the melting points of various samples of benzyl arsonic acid it was observed that in some cases the acid seemed to melt near 190° instead of the recorded melting point of 167°, which was observed in other samples. It was thought at first that this could be explained by the manner in which the samples were heated, but a series of experiments showed that this would not completely account for the two melting points of the substance. This suggested that perhaps the results were due to the existence of tautomers of the type observed in the phenyl nitromethane series:

$$\underset{\text{m.p.167}^{p}}{C_6H_5CH_2As\overset{O}{\underset{(OH)_2}{}}} \rightleftarrows \underset{\text{m.p.190}^{o}}{C_6H_5CH=As(OH)_3}$$
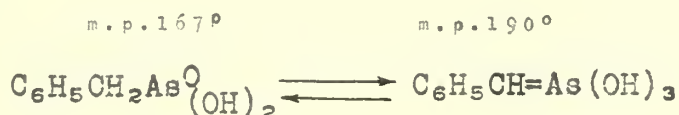
However, no method could be found for the interconversion of the "tautomers", and it was decided to prepare certain substituted benzyl arsonic acids.

Attempts were made to obtain m- and p-nitrobenzyl arsonic acids by the reaction of m- and p-nitrobenzyl chlorides with sodium arsenite under the same conditions used for benzyl chloride, but no arsonic acid could be isolated from the reaction mixture. Similar negative results were obtained with diphenyl chloromethane, and 1-phenyl-1-bromoethane. The halogenated benzyl halides reacted normally and the following halogen substituted

benzyl arsonic acids were obtained: o- and p-chlorobenzyl
arsonic acids, o- and p-bromobenzyl arsonic acids.

EXPERIMENTAL PART

Benzyl Arsonic Acid

Dehn and McGrath obtained this substance by the action of benzyl iodide on potassium arsenite in alcoholic solution at room temperature, but the great difficulty in handling benzyl iodide and the cost of the reagents indicated that this would not be a suitable method. After several experiments with benzyl chloride and potassium and sodium arsenites in boiling alcohol, it was found that excellent results could be obtained by the use of benzyl chloride and aqueous sodium arsenite at 100° to 120°. Results of this and similar experiments with various other halides are reported by Quick and Adams[12] and in general it has been found advantageous to omit the use of alcohol. The only exception to this is the case of methyl arsonic acid which separates from the alcoholic reaction mixture almost quantitatively as the disodium salt.

Preparation: In a flask provided with a mechanical stirrer and a good reflux condenser was placed a solution of 99 g. of arsenic trioxide ($\frac{1}{2}$ mole) and 124 g. of sodium hydroxide (3 moles) in 350 cc. of water. The solution was heated to 100° to 110° in an oil bath and during the course of 20 minutes 127 g. of benzyl chloride (1 mole) was added by means of a dropping funnel. The mixture was boiled vigorously for $1\frac{1}{2}$ to 2 hours longer and then cooled to room temperature. The oil which floated on the surface was extracted with a small quantity of benzene and the alkaline solution diluted with $1\frac{1}{2}$ to 2 moles of water and carefully

neutralized to litmus. This must be done by the addition of
dilute acid with good stirring between additions, or some of the
benzyl arsonic acid will be precipitated. If this procedure was
carried out properly, a slight flocculent precipitate was obtained
at this point. The neutral solution was filtered and the precipi-
tate discarded.

Dilute hydrochloric acid was added to the clear fil-
trate until it reacted acid to Congo paper, and the benzyl arsonic
acid separated out as a thick white curd. This was filtered with
suction, washed with water until free from acid, and dried in
vacuo at 90°. The yields were from 130 to 135 grams, which is
60 to 63% of the theoretical amount. The oil which is formed in
the reaction consists of benzyl alcohol (75%) and dibenzyl ether
(25%) and this accounts for 30 to 35% of the original benzyl
chloride.

Benzyl arsonic acid may be purified by crystallization
from water, 95% alcohol, or glacial acetic acid. Alcohol is to
be preferred since the acid is much more soluble in this solvent
at the boiling point, than in hot water. From water, the benzyl
arsonic acid crystallized in stout white needles; from alcohol in
small needles or plates; from glacial acetic acid in small needles.
A sample was analysed by Ewins' method:

Subs. 0.2023 g. required 35.10 cc. 0.0736 N Iodine;

Found: As = 34.41%; Calculated for $C_7H_9O_3As$: As = 34.72%.
The melting point given by Dehn and McGrath is 167° and a number
of samples were obtained with this melting point, but in certain
cases the melting point was in the neighborhood of 190° and a

number of experiments were made to determine the reason for this.

It was definitely shown that the difference was not due to water of crystallization, since material crystallized from alcohol and analysed for arsenic showed similar behavior. It was noticed that the rate of heating had a marked effect on the melting point, but this could not account for all of the discrepancies. A sample of material, for example, that crystallized from glacial acetic acid, was heated slowly in the bath and melted from $191^{\circ}-192^{\circ}$; a sample of the same material immersed at 170° and heated more rapidly melted at 192°.

The two melting points observed could be explained by the existence of the tautomeric forms,

$$-CH_2-As\overset{O}{\underset{(OH)_2}{}} \rightleftharpoons -CH=As(OH)_3$$
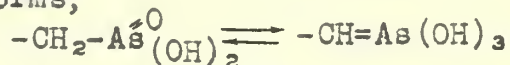
but in this case no means could be found for passing from one form to the other with certainty, and it was decided to prepare substituted benzyl arsonic acids to see if the same double melting point would be observed.

<u>Disodium Benzyl Arsonate</u>: This salt was prepared by adding two moles of sodium ethylate to a hot alcoholic solution of benzyl arsonic acid. It separates in crystalline leaflets which were filtered with suction and washed with dry ether. This salt dissolves readily in water to a clear solution, which is slightly alkaline to litmus.

<u>Lead Benzyl Arsonate</u>: The lead salt of benzyl arsonic acid was prepared by adding a solution of lead acetate or nitrate to a solution of the mono-sodium salt of benzyl arsonic acid. A heavy curdy white precipitate was obtained.

<u>Decomposition on Heating</u>: Since the nature of the products of decomposition of benzyl arsonic acid might prove of value in studying the possible tautomerism, the following experiment was carried out:

50 g. of recrystallized benzyl arsonic acid was heated in a small flask over a free flame until decomposition commenced. After the reaction was started, it proceeded without further heating, although at the end the material was heated to insure complete decomposition. The product of the reaction consisted of white arsenic trioxide, and a clear oil. The weight of the solid varied from 24-27 grams, and the liquid from 18-19 g. The latter was washed out with ether and fractionally distilled. The main product boiled from 200-210°; then the thermometer rose to 280° and a fraction was collected from 280° to 300°. The higher fraction amounted to about 10% of the liquid product.

It was apparent that no considerable amount of benzaldehyde was formed, since the thermometer rose immediately to the boiling point of benzyl alcohol and nothing passed over at 180°. From the 200-210° fraction on redistillation, a main fraction was obtained boiling from 206°-207°, which was shown to be benzyl alcohol by conversion into the p-nitrobenzoyl derivative, m.p. 83°. (83.5°-84.5° in the literature).

In order to investigate the higher boiling fraction, the combined 280°-300° fractions from the decomposition of 200 g. of benzyl arsonic acid were redistilled, and a sample of pure material boiling from 298°-302° was collected. The latter was purified by two distillations and was then used for the determin-

ation of physical constants. The analysis of the high boiling material is reported by Dehn and McGrath, and checks satisfactorily for dibenzyl ether:

Calculated for $C_{14}H_{14}O$: C = 84.85%; H = 7.07%.

Found, (by Dehn and McGrath): C = 84.65%; H = 7.95%.

Physical Constants:	Decomposition Product	Dibenzyl Ether
Specific Gravity	1.04	1.036
Refractive Index	1.5593	1.5597
Boiling Point	298°-302°	295°-298°

The above evidence proves that the high boiling fraction is not a mixture of benzyl alcohol and stilbene, but pure dibenzyl ether.[*] Dehn and McGrath state that their product decolorized bromine water, but we were unable to confirm this. A sample of high boiling material prepared according to their procedure failed to decolorize bromine water, and our sample of dibenzyl ether did not decolorize this reagent.

In order to see whether benzaldehyde might be formed under some other circumstances, a sample of benzyl arsonic acid was moistened with water and heated in a 200 cc. flask over a free flame. An ill-smelling gas was formed during the reaction, and the distillate consisted of water and an oil, smelling strongly of benzaldehyde. The water was separated from the heavier oil, and the latter was shaken with sodium bisulfite solution and ether added to take up the insoluble portion. The bisulfite

[*] In order to show that the dibenzyl ether obtained was not formed by a secondary reaction from benzyl alcohol and arsenic trioxide, 75 g. of benzyl alcohol and an equal weight of arsenic trioxide were boiled together for 45 minutes under reflux. The mixture after cooling and extraction with ether was distilled and no dibenzyl ether was found.

extract was made alkaline with sodium carbonate, and steam dis-
tilled, when a clear white oil having the odor of benzaldehyde
passed over. This was extracted with ether and identified as the
phenyl hydrazone, m.p. 154°-155°, (m.p. 155°-156°, of phenyl hydra-
zone from known benzaldehyde). A mixed melting point of these two
substances was unaltered. This proves conclusively that benzalde-
hyde can be formed when benzyl arsonic acid is decomposed by heat,
but it is not one of the main products of the reaction. The
following equation is suggested for its formation:

$$3\ C_6H_5CH_2AsO_3H_2 \longrightarrow 3C_6H_5CHO + As_2O_3 + AsH_3 + 3H_2O$$
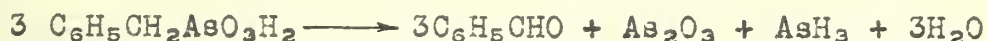
The arsine formed in this reaction accounts for the ill-smelling
gas which is evolved, and its decomposition by heat would account
for the deposit of metallic arsenic observed in the flask and con-
denser tube.

Decomposition by Mineral Acids: Concentrated hydrochloric acid
decomposes benzyl arsonic acid in the cold with the formation of
benzyl chloride and arsenic chloride. Strong sulfuric acid decom-
poses it in the cold with the formation of arsenious acid and a
gummy material. If the benzyl arsonic acid is dissolved in hot
water and a few cc. of strong sulfuric acid added and the mixture
boiled for a short while, the decomposition is quantitative, as
stated by Dehn and McGrath:

$$C_6H_5CH_2AsO_3H_2 \xrightarrow[\text{sulfuric}]{\overset{100^{\circ}}{\text{dilute}}} C_6H_5CH_2OH + H_3AsO_3$$
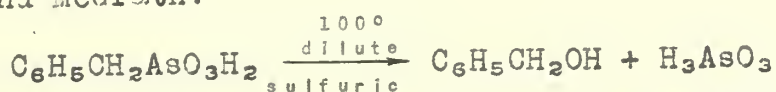
By using the following procedure it was found that a simple quan-
titative determination of benzyl arsonic acid could be made:-

Samples of pure benzyl arsonic acid weighing 0.3 to
0.4 g. were placed in a 500 cc. erlenmeyer flask, 100 cc. of water

added and the acid dissolved by boiling on a wire gauze. After
cooling, 10 cc. of concentrated sulfuric acid were added and the
solution boiled gently for 20 - 30 minutes. It was then cooled,
neutralized with alkali and faintly acidified with sulfuric acid.
Sodium bicarbonate was then added and the arsenious acid titrated
with standard iodine in the usual way.

Weight of Sample	Iodine Solution	Arsenic Found
0.4164 g.	52.63 cc	34.88 %
0.2109 g.	26.54 cc	34.73 %
0.1732 g.	21.73 cc	34.63 %
0.1874 g.	23.52 cc	34.64 %
0.2013 g.	25.36 cc	34.69 %
0.2425 g.	30.58 cc	34.80 %

Calculated for Benzyl Arsonic acid .... 34.72 %

Average of six determinations above ...... 34.73 %

Iodine solution = 0.0736 Normal.

Using this method, the solubility of benzyl arsonic acid in water
at 25° was found to be 0.369 g. per 100 cc. of solution. Dehn
and McGrath found 0.34 g. at 23.5° and 0.39 at 27°. Interpolation
of their results for 25° gives 0.368 g. per 100 cc., which is in
close agreement with the above result.

Benzyl Arsine

This substance is described by Dehn, who obtained it
in the usual manner by the reduction of the arsonic acid with
amalgamated zinc and strong hydrochloric acid. In practice it
was found advisable to mix the benzyl arsonic acid with water, so

that the acid used would not be sufficiently strong to decompose it.

Preparation: In a flask provided with a mechanical stirrer and an efficient bulbed reflux condenser were placed 100 g. of pure benzyl arsonic acid, 750 g. of amalgamated zinc dust, 500 cc. of water and 500 cc. of ether. This mixture was stirred vigorously and concentrated hydrochloric acid was allowed to run in slowly from a dropping funnel, and ether was added from time to time to maintain the original amount of about 500 cc. After two or three days the ethereal layer was drawn off into a 250 cc. Claissen flask from which it was distilled in portions. The residue consisted of benzyl arsine and water, and was distilled under reduced pressure in an atmosphere of nitrogen. Water first distills off and then the benzyl arsine comes over as a clear white liquid, gradually becoming yellow on standing. The boiling points observed were 95° at 30 mm., and 90° at 24 mm. Dehn reported 140° at 260 mm. The yield was $37\frac{1}{2}$ g. which is 50% of the theoretical amount.

Reaction with Benzaldehyde: $37\frac{1}{2}$ g. of benzyl arsine was mixed with 47 g. of benzaldehyde (2 moles) and a few drops of strong hydrochloric acid. The mixture became quite warm and formed a pasty mass. The latter was washed with dry ether, but only an insoluble red product, benzaldehyde, and benzyl arsonic acid could be identified in the mixture. A repetition of the reaction gave the same results.

Substituted Benzyl Arsonic Acids

The instability of benzyl arsonic acid toward mineral acids limits the reactions which can be applied to this substance

and therefore it was decided to try certain substituted benzyl halides in Meyer's reaction, to obtain the desired derivatives.

Experiments with m-nitrobenzyl chloride, p-nitrobenzyl chloride, diphenyl chloromethane, and 1-phenyl-1-bromoethane did not lead to the desired arsonic acids, but the halogenated benzyl halides were found to give the corresponding halogenated benzyl arsonic acids in good yields.

4-Chlorobenzyl Arsonic Acid

Preparation: p-Chlorobenzyl chloride was prepared by the action of chlorine in the sunlight on an excess of pure p-chlorotoluene, heated to boiling. The product was purified by distillation under atmospheric pressure and then in vacuo. The reaction was carried out as described for benzyl arsonic acid, except that a 20% excess of the sodium arsenite was used. The product separated out as a mass of fluffy white crystals, in a yield of 60 per cent of the theoretical amount. p-Chlorobenzyl arsonic acid may be crystallized from water or dilute alcohol; it is quite soluble in hot 95% alcohol and does not separate on cooling; it is insoluble in ether and organic solvents. m.p. 184°.

Analysis: (Robertson's method)

Subs. 0.2482, 0.2475 g.; required 24.52, 24.23 cc 0.0808 N I.

Calc. for $C_7H_8O_3ClAs$: As = 29.92%; Found: As = 29.66%, 29.93%. This acid is decomposed by warm mineral acids in the same way as benzyl arsonic acid; with strong hydrochloric acid, p-chlorobenzyl chloride is formed.

3-Chlorobenzyl Arsonic Acid

In considering the preparation of the halogen substituted benzyl arsonic acids it was noted that the halogenated benzyl bromides were more easily prepared than the chlorides, and since the former react equally well with sodium arsenite, it was decided to use them. A great deal of difficulty is experienced in handling these substances since they are very powerful lachrymators, and to avoid this a simplified method was employed.

<u>General Procedure</u>: One mole of the pure halogenated toluene was heated to boiling in the sunlight, and slightly less than one mole of bromine was slowly added through a dropping funnel. The reaction mixture after addition of all of the bromine was allowed to cool, and the product washed with ice water. This sometimes caused the material to solidify. The water was separated by decantation, and the washing repeated. The crude halogenated benzyl bromide was then treated with a solution of 1.2 moles of sodium arsenite, and boiled under reflux with good stirring. The heating was continued for 6 to 8 hours, and the course of the reaction followed by titration of samples of the solution from time to time. The reaction is 60% to 75% complete after the time mentioned.

After cooling, the reaction mixture was extracted with benzene to remove the oily layer and the alkaline solution was treated with decolorizing charcoal and filtered. The clear filtrate on acidification with 20% sulfuric acid* gave a white curdy

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* Sulfuric acid is used in preference to hydrochloric acid, since a trace of the latter if not removed by the washing, will cause the formation of lachrymating substance when the crude acid is dried.

precipitate of the halogenated benzyl arsonic acid.

Preparation: Pure o-chlorotoluene was converted to o-chlorobenzyl bromide and reacted with sodium arsenite according to the general directions. The reaction was 60% complete after four hours, and no appreciable decrease of iodine titration was observed after an additional four hours heating. The o-chlorobenzyl arsonic acid separated out as white crystalline flakes, which may be recrystallized from water or dilute alcohol. From water it is obtained in small white plates, m.p. 157-158°.

Subs. 0.2008, 0.1970 g. required 17.98, 17.86 cc. 0.0893 N I

Calc. for $C_7H_8O_3ClAs$: As = 29.92%. Found: 30.00%, 30.37%.

4-Bromobenzyl Arsonic Acid

Preparation: Using p-bromotoluene as described in the general procedure, the reaction of the p-bromobenzyl bromide with sodium arsenite was observed to be 75% complete after eight hours. The p-bromobenzyl arsonic acid was obtained as beautiful white needles from dilute alcohol; m.p. 178°-180°.

Subs. 0.2497, 0.2500 g. required 19.42, 19.50 cc. 0.0893 N I

Calc. for $C_7H_8O_3BrAs$: As = 25.42%. Found: 25.46%, 25.53%.

2-Bromobenzyl Arsonic Acid

Preparation: Starting with o-bromotoluene, the general procedure was followed and the reaction between o-bromobenzyl bromide and sodium arsenite was observed to be 66% complete after eight hours. The acid was obtained in the usual manner, and was purified by recrystallization from dilute alcohol, from which it separated in
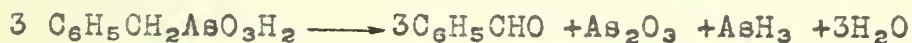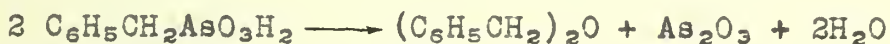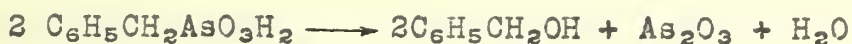
small white plates; m.p. 188°-190°.

Subs. 0.2493, 0.2490 g. required 19.40, 19.51 cc. 0.0893 N I

Calc. for $C_7H_8O_3BrAs$: As = 25.42%.   Found: 25.53%, 25.65%.

SUMMARY

A convenient method was found for the preparation of large quantities of benzyl arsonic acid, and an interesting observation was made on the melting point of this substance.

The products of the decomposition of benzyl arsonic acid by heating were investigated and the following equations were found to represent the reactions more accurately than any previously suggested:

$$2\ C_6H_5CH_2AsO_3H_2 \longrightarrow 2C_6H_5CH_2OH + As_2O_3 + H_2O$$

$$2\ C_6H_5CH_2AsO_3H_2 \longrightarrow (C_6H_5CH_2)_2O + As_2O_3 + 2H_2O$$

$$3\ C_6H_5CH_2AsO_3H_2 \longrightarrow 3C_6H_5CHO + As_2O_3 + AsH_3 + 3H_2O$$

Benzyl arsine was condensed with benzaldehyde, but no simple compound of the type, $R-As(CHOH-R)_2$, could be isolated from the reaction mixture. Benzyl arsonic acid and an insoluble red product were formed.

A simple method has been devised for the quantitative determination of arsonic acids of the benzyl series, based on their decomposition by hot aqueous sulfuric acid.

The following halogen substituted benzyl arsonic acids were prepared: o- and p-chlorobenzyl arsonic acid, and o- and p-bromobenzyl arsonic acids.

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Vita

The writer was born in Chicago, Illinois, on August 9, 1900. He attended the Lincoln School in this city from 1906-1913 and was graduated from the Lane Technical High School in 1916. He attended the Lane Junior College during 1916 and 1917 and entered the University of Illinois in 1917. He was graduated from the latter institution in 1919 with the degree of Bachelor of Science in Chemistry, and received the degree of Master of Science in 1920. The following appointments were held in the University of Illinois:

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